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Original research

Elimination of warm ischemia using the Ice Bag Technique does not decrease delayed graft function

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ABSTRACT

Background: Warm ischemic time (WIT) in kidney transplantation has significant effects on graft survival, function, and postoperative morbidity. We utilized the Ice Bag Technique (IBT) to determine if eliminating WIT would decrease the incidence and length of delayed graft function (DGF) in our cohort.
Methods: We conducted a prospective study of 150 kidney transplants. We compared the elimination of WIT with IBT to traditional methods. Data was analyzed using non-parametric statistical tests.
Results: 66 of the 134 patients underwent transplantation using IBT. 28 right kidneys, 34 left kidneys, and 4 dual kidneys were implanted successfully. Patients with a body mass index (BMI) as high as 41 were transplanted. Kidneys with up to three arteries and two veins, and kidneys up to 15.5 by 9 cm in size were safely transplanted into either iliac fossa. Despite the complete elimination of WIT, there was no difference in DGF, length of DGF, length of stay graft rejection, graft survival, patient survival, or wound or urologic complications between groups ($p > 0.05$).
Conclusions: The elimination of warm ischemic time using the IBT does not appear to reduce the incidence or length of DGF in this cohort. The technique may be useful for cases with prolonged anastomosis time (AT), but further studies with larger cohorts are required to determine whether it decreases DGF.

1. Introduction

It is impossible to transplant an organ without causing ischemia and microcirculatory disturbance. These insults are established causes of reperfusion injury and functional impairment [1–3]. Ischemia and reperfusion injury (IRI) are associated with an increased rate of acute rejection, primary non-function (PNF), delayed graft function (DGF), initial poor graft function (IPGF), and late graft failure [1–4].

WIT refers to the time necessary to perform the vascular anastamoses during kidney transplantation [1,4]. While WIT is an accepted risk factor for DGF, we do not know the safe upper limit. DGF is defined as the requirement of dialysis within seven days of transplantation. It is a negative prognostic indicator for long-term allograft survival and is also associated with significant costs. Attempts to minimize WIT include wrapping the kidney in an ice-soaked laparotomy pad. Other techniques include using an RAYTEC sponge (Johnson & Johnson, New Brunswick, NJ, USA), stockinette, cooling jacket, or clear sterilized bag [5]. Some surgeons eschew this technique, preferring to simply suture the vessels as quickly as possible. However, this approach may lead to technical errors, excessive bleeding, worse long-term outcomes, and a poor learning experience for the resident staff [1]. The ice bag technique is a method developed in the 1990's to reduce WIT that was largely abandoned before being studied in the literature. This technique may potentially lead to less DGF. The aim of this study was to evaluate the effect of the IBT on incidence and length of DGF. We also sought to determine its effect on wound and urologic complications as well as patient and graft survival.

2. Materials and methods

We conducted an Institutional Review Board – approved prospective study of renal transplants performed between January 2010 and June 2011. 150 renal transplants were identified after excluding allografts from living or infant donors. These were excluded to provide uniformity to our cohort and because they comprised an extremely small proportion of transplants. We also wanted to show that the technique is safe with longer vessels,

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which are more likely found in deceased donors than living donors. We divided subjects into three arms: IBT, non-IBT due to surgeon preference, and non-IBT for anatomic reasons. Informed consent was waived by the local ethics committee. Cases performed by the surgeon who preferred not to use the IBT served as the control group. Patients in the anatomic limitation group were excluded from statistical analysis. Reasons for exclusion from the IBT included cut or short renal arteries or veins, difficult arterial course, duplicate arteries, recipient BMI, and limited operative space (Table 1). The follow-up for these patients was one year, which was chosen because our primary endpoint, DGF, would manifest within that time frame.

Donor variables recorded include donor type (donation after cardiac death or DCD, donors after neurologic determination of death or DND, expanded criteria donors or ECD, and combined ECD/DCD donors), donor gender, donor age, kidney side, size, number of vessels, terminal creatinine and use of the machine perfusion pump. We classified donor type by the Organ Procurement and Transplantation Network (OPTN) definitions. We also examined recipient demographics including body mass index (BMI), comorbidities such as diabetes and hypertension, and primary renal disease. Intraoperative parameters included WIT, cold ischemic time (CIT), and operative site. We defined WIT, also referred to as AT, as time from removal of the kidney from storage to reperfusion with or without IBT. It is important to note that WIT was eliminated with the IBT. Primary endpoints included incidence and length of DGF. The length of DGF was defined as the duration between transplant date and last dialysis session. Secondary endpoints included creatinine levels on postoperative days 10 and 365, graft rejection, graft and patient survival, length of hospital stay (LOS), wound complications and urologic complications. Creatinine levels at postoperative day 10 were chosen as this is the usual postoperative nadir value. We also collected data on postoperative day 365 creatinine as it is routinely collected by UNOS and is an excellent predictor of long-term allograft outcome. Renal allograft loss was defined as death with a functioning graft, allograft nephrectomy or resumption of dialysis. Wound complications included fascial dehiscences, wound dehiscences, and wound infections. Wound infection was defined as infection of the skin or subcutaneous tissues surrounding the surgical wound. Urologic complications examined include urosepsis and urine leaks. Results were compiled into a series of Excel databases to be analyzed at the end of the specified time period. Due to the small size of the group, patients in the anatomical exclusion cohort were unable to be statistically compared to the patients in the IBT and non-IBT cohort and were thus excluded from statistical analysis.

All procedures were in accordance with the Helsinki Declaration of 1975.

2.1. The Ice Bag Technique

After back table preparation, the allograft was placed in an ice-filled bag with an outlet for the renal artery and vein. A Kelly clamp was employed to maintain the fluid and ice in place and to function as a handle (Fig. 1). The handle was always placed on the inferior (ureteral) side of the graft for orientation. A penetrating towel clamp affixed the kidney to one side of the wound while the anastomoses were performed (Fig. 2). After completion of the anastomoses, the vascular clamps were removed and the bag was cut and passed off the field. At no time was there evidence of loss of the cooling properties of the ice bags or frostbite leading to injured kidney parenchyma in the IBT group.

Table 1
Reasons for anatomic exclusion.

Anatomic reasons for exclusion	Number (n)
Arteries cut	1 (6%)
Short arteries	3 (18%)
Difficult arterial course	1 (6%)
Ice bag failure	3 (18%)
Short renal vein	1 (6%)
Duplicate arteries	2 (12%)
Too small space	1 (6%)
BMI	3 (18%)

2.2. Patient management protocols

All patients were immunosuppressed with Prograf (Tacrolimus, Astellas Pharma, Deerfield IL), Cellcept (Mycophenolate Mofetil, Roche, Nutley NJ) and prednisone. Anti-thymocyte globulin (ATG, Genzyme) was the most common agent used for induction therapy, followed by the IL-2 receptor antibody (Daclizumab). ATG was dosed at 1.5 mg/kg per day for 4–7 days starting intraoperatively through a central line and titrated for leukopenia, thrombocytopenia or other side effects attributed to the induction. The goal dose ranged between 5 and 6 mg/kg. Acetaminophen, diphenhydramine and steroids were given before all infusions. All patients were started on Mycophenolate Mofetil with doses ranging from 1 to 2 g per day. The dosage was titrated for gastrointestinal side effects and leukopenia. Patients received methylprednisolone 400–500 mg IV intraoperatively followed by a prednisone taper to 30 mg daily by day 7, 20 mg daily by day 30 and 5 mg daily by day 90. Tacrolimus was started by day 4. Target trough levels ranged between 5 and 12 ng/ml. For Pneumocystis jiroveci pneumonia prophylaxis, all patients received one single strength trimethoprim/sulfamethoxazole daily for at least 6 months post transplant, and 3 months after

Fig. 1. Ice Bag Technique: The kidney is introduced into the bag with ice and a small hole was made near the hilum through which the renal artery and vein were passed. A Kelly clamp was used to maintain the fluid and ice in place as a handle.

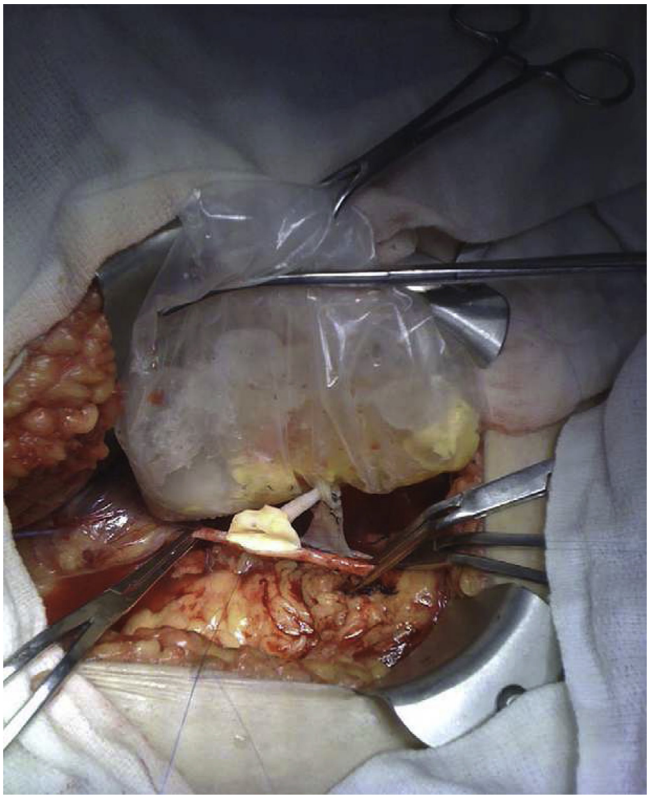

Fig. 2. Ice Bag Technique during anastamosis. The kidney placed in an ice bag is introduced into the field with a penetrating towel clamp affixed to one side of the wound while the anastamoses are performed.

every rejection episode. In patients with sulfa allergies Dapsone or aerosolized pentamidine was employed. Fungal prophylaxis was provided by oral clotrimazole or nystatin for 2 months post-transplant. For Cytomegalovirus (CMV) prophylaxis all patients received at least 3 months of valgancyclovir with doses ranging from 450 mg every other day to 900 mg daily, depending on renal function and established risk factors. CMV prophylaxis was re-instituted for three months after every rejection episode.

All rejection episodes were biopsy proven and the Banff 97 classification was used to grade each biopsy specimen. Grade 1 cellular rejections were treated with intravenous methylprednisolone. Recalcitrant Grade 1 and all Grade 2 cellular rejections were treated with 5–6 mg/kg of ATG. Intravenous pulse steroids, ATG, intravenous immunoglobulin and plasmapheresis were employed for clinically significant antibody mediated rejections.

2.3. Statistical analysis

SAS was used for the statistical analysis. A Wilcoxon rank sum test and Chi-square test were applied for numerical and categorical data respectively because most of the risk factors were normally distributed. Non-parametric statistical methods were used to determine whether or not the ice bag technique had an effect on the incidence and duration of DGF. We defined the null hypothesis as no difference between the IBT and non-IBT populations with respect to incidence and length DGF. Kaplan–Meier analysis was also used to analyze graft survival data.

Due to the small sample size and many DGF associated risk factors, univariate logistic regression was utilized to reduce the dimension of risk factors. After univariate logistic regression analysis, significant risk factors were included in a multivariate logistic regression model. For the two-group comparison, categorical variables were analyzed using the Fisher exact and Chi-square tests. Continuous variables were analyzed using nonparametric methods because our continuous variables were not normally distributed. A p-value of 0.05 was considered statistically significant.

3. Results

There were a total of 134 transplants in the analysis, 66 in the ice bag group and 68 in the control group. Baseline donor and recipient demographics as well as perioperative variables are depicted in Tables 2 and 3. There was no difference in recipient characteristics, perioperative variables or postoperative outcomes between the two groups.

Table 2
Donor variables.

Variable		Total observation numbers, N, are 134		
		IBT ($N_1 = 66$) (49%)	Non-IBT ($N_2 = 68$) (51%)	P-value
Donor Type, n (%)	DCD	13 (19.7%)	25 (36.8%)	0.03
	DND	42 (63.6%)	37 (54.4%)	0.28
	ECD	6 (9.1%)	5 (7.4%)	0.71
	ECD/DCD	4 (6.1%)	0 (0%)	0.04
Donor Kidney, n (%)	Right	28 (42.4%)	35 (51.5%)	0.29
	Left	34 (51.5%)	33 (48.5%)	0.73
	Both	4 (6.1%)	0 (0%)	0.04
Gender, n (%)	Male	50 (75.8%)	42 (61.8%)	0.08
	Female	16 (24.2%)	26 (38.2%)	
Number of arteries in donated kidney, n (%)	One	54 (81.8%)	56 (82.4%)	0.94
	Two	11 (16.2%)	9 (13.2%)	0.58
	Three	1 (1.5%)	2 (2.9%)	0.57
	Four	0 (0%)	1 (1.5%)	0.32
Number of veins in donated kidney, n (%)	One	62 (93.9%)	63 (92.6%)	0.77
	Two	4 (6.1%)	5 (7.4%)	
Normal number of arteries and veins in donated kidney, n (%)	Normal	52 (78.79%)	53 (77.94%)	0.91
	Multiple	14 (21.21%)	15 (22.06%)	
Donor Age (y), Mean (SD)		42.8 ± 3.47 (14.09)	40.25 ± 3.61 (14.92)	0.5
Terminal Creatinine, Mean (SD)		1.02 ± 0.12 (0.42)	1.03 ± 0.09 (0.51)	0.98
Machine perfusion, n (%)		16 (44.4%)	20 (55.6%)	0.49

DCD = Donation after cardiac death; DND = donor after neurologic death; ECD = expanded donor criteria; SD = standard deviation.

Table 3
Recipient and perioperative variables.

		Total observation numbers, *N*, are 134		*P*-value
		IBT ($N_1 = 66$) (49%)	Non-IBT ($N_2 = 68$) (51%)	
Age at time of transplant (years), Mean (SD)		54.11 ± 2.6 (10.59)	54.89 ± 2.79 (11.5)	0.62
Kidney Sizes (Length × Width) Cm, Mean		11.63 × 5.36 ± 1.34 × 1.01	11.53 × 5.63 ± 1.32 × 1.00	0.43
BMI (kg/m2), Mean (SD)		26.67 ± 1.3 (5.22)	26.97 ± 1.13 (4.59)	0.98
Site of incision, *n* (%)	Right	55 (83%)	59 (87%)	0.33
	Left	10 (15%)	8 (12%)	
	Midline	1 (2%)	1 (1%)	
EBL (mL), Mean (SD)		191.23 ± 22.86 (82.97)	179.3 ± 21.12 (84.23)	0.37
WIT (min), Mean (SD)		30.46 ± 1.33 (5.00)	29.56 ± 1.27 (5.08)	0.19
CIT (hours), Mean (SD)		13.73 ± 1.35 (5.45)	14.69 ± 1.35 (5.56)	0.36
Total Procedure Time (min), Mean (SD)		191.92 ± 15.91 (64.19)	177.97 ± 8.16 (33.7)	0.43
Creatinine at POD 10, Mean (SD)		3.75 ± 0.76 (3.10)	4.16 ± 0.83 (3.44)	0.43
1 Year Creatinine, Mean (SD)		1.64 ± 0.2 (0.7)	1.91 ± 0.43 (1.5)	0.19
DGF		27 (52%)	25 (48%)	0.67
AVG Length DGF, Mean (SD)		7.89 ± 3.59 (9.07)	10.25 ± 3.99 (9.45)	0.21
Rejection within 1 year Total, *n* (%)		6 (9.1%)	10 (14.7%)	0.32
Length of Stay, Mean (SD)		11.38 ± 2.01 (8.16)	10.52 ± 1.52 (6.23)	0.41
Recipient Deaths (1 Year), *n* (%)		5 (7.6%)	2 (2.9%)	0.23
Graft Survival (1 Year), *n* (%)		60 (90.9%)	64 (94.1%)	0.48
Recipient HTN Status		50 (76.92%)	57 (83.82%)	0.32
Recipient diabetes status		27 (40.91%)	26 (38.81%)	0.80
Wound complication		9 (13.64%)	3 (4.41%)	0.07*
Urologic complications		3 (4.55%)	1 (1.47%)	0.36*

*Fisher exact test.
CIT = Cold ischemic time; WIT = Warm ischemic time; EBL = estimated blood loss.
SD = Standard deviation, BMI = Body mass index, IgA = Immunoglobulin A.
*Subject excluded from length of stay due to non transplant complications.

Table 4a
Univariate analysis of risk factors for delayed graft function.

Variable	*p*-value
AA	0.4822
Ice Bag	0.6710
WIT	0.2336
CIT	0.1630
ECD	0.6528
Obesity	0.9597
EBL	0.3128
Normal vessel	0.3724
Donor terminal creatinine	0.4731
Pumped	0.3512
Total duration of operation	0.3070
Donor age	0.0233
DCD	0.0301
ECD/DCD	0.6526
DND	0.0136

Table 4b
Multivariate analysis of risk factors for delayed graft function.

Variable	*p*-value
Intercept	0.0628
Donor age	0.0464
DCD	0.1942
DND	0.9318

3.1. DGF data

The rate of DGF in this cohort was 52% for IBT and 48% for non-IBT. The mean length of DGF was 7.9 days for IBT and 10.2 days for non-IBT. The difference in the rate and length of DGF between groups was not statistically significant ($p = 0.67$ and $p = 0.21$, respectively) (Table 3). The use of the IBT did not correlate with increasing or decreasing rate or length of DGF ($p > 0.05$). In univariate analysis, donor age, ($p = 0.02$), DCD ($p = 0.03$) and DND ($p = 0.01$) were significantly associated with DGF (Table 4a). Multivariate analysis predicted only donor age ($p = 0.046$) to have an effect on DGF (Table 4b).

3.2. Ischemic times

We measured WIT/AT for both groups, although WIT was technically eliminated with IBT. WIT was 30.46 min in the IBT group and 29.56 min in the non-IBT group. There was no difference in WIT or CIT between the two groups ($p = 0.19$ and $p = 0.36$, respectively).

3.3. Patient outcomes

There was no difference in mean length of stay between the two groups ($p = 0.41$). The difference in incidence of wound complications between groups was also not statistically significant ($p = 0.07$). The IBT group had two cases of urosepsis and one urine leak, while the control group had one case of urosepsis and no urine leaks. There was no statistical difference between the two groups ($p = 0.36$). There was no statistically significant difference in one-year rejection rates between the two groups ($p = 0.32$). There was no significant difference in graft survival at 1 year ($p = 0.48$) or patient death at 1 year ($p = 0.23$) between the two groups. Kaplan–Meier analysis confirmed no difference in graft survival.

3.4. Anatomic exclusion arm

A summary of the characteristics of cases in the anatomic exclusion arm can be found in Table 1. Of the 15 patients in this cohort, the most common reason for exclusion from IBT was vascular anomalies. One patient was excluded because the renal artery was cut during procurement. Three patients were excluded due to short renal arteries leading to difficult anastomoses. Another three patients had a tortuous arterial course from the hilum of the kidney. One patient had a short renal vein, which made ice bag preparation and anastomoses difficult. Another patient was

excluded because the ice bag could only be used for the vein but not for the artery. In three cases, the ice bag was damaged during the anastomosis. Another patient had a small iliac fossa, which made it difficult to position the kidney appropriately.

4. Discussion

Ischemic reperfusion injury associated with WIT leads to DGF. The consequences of prolonged DGF include increased length of hospital stay and costs associated with treatments such as dialysis. While WIT is a known risk factor for DGF, the upper limit of WIT beyond which allograft dysfunction arises is unknown. Our study shows that eliminating warm ischemic time with the use of the ice bag technique does not reduce the incidence or length of DGF in DCD, DND, ECD or ECD/DCD donors in our cohort. The IBT is also not associated with decreased length of stay or a decrease in wound or urologic complications, graft rejection or patient death.

Ischemic reperfusion injury is thought to result from an imbalance in metabolic supply and demand within the ischemic organ [6]. Ischemia results in tissue hypoxia and microvascular dysfunction. Reperfusion extends the insult by activation of innate and adaptive immune responses and cell death programs [7]. WIT limits as low as 30 min [8] and as high as 50 min [9] have been advocated for acceptable graft function. Also problematic is the fact that no large study has systematically examined the effect of donor category on WIT. Importantly, WIT is not consistently documented in the UNOS database. While the true upper limit of WIT is unknown, prolonged WIT has an established association with delayed graft function and adverse outcomes [8].

Many studies have attempted to document the importance of reducing WIT. Feuillu et al. [10] showed that allograft temperature rises 0.48 °C per minute and is 26.7 °C by the end of the anastomosis, therefore emphasizing the importance of meticulous ex vivo preparation and minimal anastomosis time. Szostek et al. [11] observed an increased incidence of delayed graft function when kidney temperature was greater than 15 °C, suggesting that increased temperature is associated with developing DGF. Gavela Martinez et al. retrospectively studied patients who developed DGF and found prolonged anastomosis time to be a risk factor [12].

To prevent graft damage associated with warm ischemia, various methods of reducing WIT have been reported. A Polish group attempting to eliminate WIT described a complex polyethylene receptacle that requires six hours to sterilize and contains three separate containers allowing for storage and performance of anastomoses [5]. This method is too complex for routine practice, and the article does not report an association between use of the device and lower rates of DGF. By contrast, the ice bag is a relatively simple method of eliminating WIT with negligible equipment, preparation time and manipulation of treatment protocols. A recently study described the use of regional hypothermia during robotic kidney transplantation to reduce WIT during the learning curve required for robotic vascular anastomoses [13]. However, this study focused on technique and did not address DGF.

While our study shows that eliminating WIT with the IBT did not provide any advantage in our cohort, it may still be an important technique. Because the upper limit of WIT that leads to uncomplicated kidney transplantation is unknown, reducing WIT with the ice bag technique may still be of some benefit. Furthermore, there are instances where anastomosis time is excessive due to technical or anatomic difficulties. Recipients with large body habitus and allografts with multiple vessels may have prolonged AT. Our study displays that the IBT can successfully be used in dual kidney transplants, multiple organ transplants, and kidneys with multiple vessels. We were able to transplant a right or left donor kidney into either fossa using the IBT. The technique was successful in large kidneys and recipients with a BMI as high as 41. In these cases, the IBT can function to preserve the organ during a long anastomosis. It is a transparent device, allowing for excellent orientation of the kidney and visualization of the anastomoses. Total operative time was not prolonged. While this study served as a proof of principle, we are planning a randomized controlled trial with larger sample sizes to determine whether the IBT has any role in decreasing DGF in kidney transplantation.

4.1. Strengths and limitations

Strengths of this study include its prospective design and one-year follow-up period. Furthermore, our cohort size was large enough to perform statistical analysis.

There were several limitations to our study. The transplants in the two arms were performed by different surgeons, introducing the possibility of confounding by differences in surgeon preference and technique. The control group was generally comprised of surgeons who did not favor the IBT, introducing significant bias. We did not have long-term outcomes on this cohort and therefore cannot comment on possible complications several years after transplantation. Also, despite affording the possibility of statistical analysis, our cohort size was too small and too heterogeneous to provide clinically meaningful conclusions. In order to statistically address the effect of the IBT on incidence of DGF, we would need at least 650 patients to achieve adequate power for statistical analysis. Lastly, our study design was not a randomized prospective clinical trial, because our control group was based on surgeon preference. Hence, potential bias may have been introduced in addition to relative lack of power and instability of the univariate and multivariate models.

5. Conclusion

Elimination of WIT using the IBT seems not to affect incidence or length of DGF in our cohort. The technique is not associated with decreased postoperative complications. Various types of kidney transplants can be safely performed with this technique, and it may be useful in cases with prolonged anastomosis time due to anatomic or technical difficulties. Larger studies with IBT will be necessary in order to truly determine whether the elimination of WIT decreases the incidence and length of DGF.

Conflict of interest

The authors have no conflict of interest to disclose.

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Contributions

Farah Karipineni: analyzed data, wrote paper
Stalin Campos: performed research
Afshin Parsikia: collected data
Joel Durinka: analyzed data
Po-Nan Chang: analyzed data
Kamran Khanmoradi: performed research
Radi Zaki: performed research
Jorge Ortiz: performed research, collected data

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